REMARKS

With this Amendment, claims 54 and 73-99 are pending. Claims 1-37 were canceled without prejudice or disclaimer in Applicants' Amendment dated January 10, 2006. Claims 38-53 and 55-72 were canceled without prejudice or disclaimer in Applicants' Response dated April 17, 2008. Claims 75-77 and 82-87 have been withdrawn from consideration by the Examiner as being drawn to non-elected species. Claims 54, 78, 79, 93, 95, 96, 98 and 99 have been amended. New claim 100 has been added. Support for the amendments to claim 54 can be found at least throughout the specification as filed, particularly at page 17, line 18. Support for the amendments to claims 78, 79, 98 and 99 can be found throughout the specification as filed, particularly at page 20, line 8, and at page 22, line 27 - page 23, line 9. Support for the amendment to claim 93 can be found at least in the specification as filed, particularly at page 19, line 24 - page 20, line 3. Support for the amendment to claim 96 can be found at least in the claims as originally filed and in the specification as filed, for example, at page 23, line 19. Support for new claim 100 can be found can be found throughout the specification as filed, particularly at page 20, line 8, and at page 22, line 27 - page 23, line 9. No new matter has been added by way of the present amendments.

The amendments to the specification have been made to the priority claim and to state the date of the deposit of the hybridoma cell line of accession number DSM ACC2542 and the complete address of the depository. No new matter has been added by way of the present amendments.

I. Election of Species

Applicants thank the Examiner for acknowledging Applicants' election without traverse of a CD3/CD14 expressing cell as the species of tolerance inducing cell, and autoimmune disease as the species of disease associated with disturbed self-tolerance. Upon the finding of allowable subject matter, Applicants reserve the right to consideration of claims to additional species. Applicants understand that Claim 54 is considered generic with respect to all species

elections and is under consideration to the extent that it reads on the elected species. Claims 75-77 and 82-87 may be examined in this application should the elected species be found allowable.

II. Claim for Priority

Applicants thank the Examiner for acknowledging Applicants' claim for priority. Applicants have amended the priority statement to indicate how the instant application relates to U.S. Application No. 10/520,931.

III. Response to Rejections

A. Rejection Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 93-96 and 98 as allegedly being unpatentable under 35 U.S.C. § 112, first paragraph. The Examiner has stated that the specification allegedly does not contain a written description of the invention. Applicants respectfully traverse this rejection.

1. Claims 93-95

Applicants thank the Examiner for stating that page 20 of the instant specification "provides support for a method of administering a tolerance inducing cell composition comprising lymphocytes..." Office Action at page 3. The Examiner further states that "the disclosure by the specification of culturing tolerance inducing cells in vitro with lymphocytes to expand CD4+CD25+ regulatory T cells for administration to a subject has a narrower scope than the instant claims." *Id.* The Examiner then concludes that "the specification only discloses co-culturing a tolerance inducing cell with a lymphocyte to generate said administered regulatory T cells." *Id.* Applicants respectfully disagree with the Examiner's conclusion. However, solely in order to advance prosecution, and not in acquiescence to the Examiner's rejections, Applicants have amended claim 93 to recite that said lymphocyte is co-cultivated with a self-tolerance

inducing cell to induce formation of regulatory T lymphocytes such as CD4+/CD25+ lymphocytes.

The Examiner further alleges that "the disclosure by the specification of culturing tolerance inducing cells in vitro with lymphocytes to expand CD4+CD25+ regulatory T cells for administration to a subject has a narrower scope than the instant claims." *Id.* The Examiner concludes that "the specification only discloses co-culturing a tolerance inducing cell with a lymphocyte to generate said administered regulatory T cells." Applicants respectfully disagree with the Examiner's contentions and conclusion. In the specification at page 19, lines 27-30, the specification discloses that lymphocytes from recipient animals were incubated with immune suppressive cells from the respective donor animals *in vitro*. Furthermore, in Example 7 (on page 53 of the specification as filed), animals were injected with lymphocytes from a recipient animal that had been previously directly co-cultivated with transplant acceptance inducing cells. Thus, the specification clearly discloses a method of administering a tolerance inducing cell composition comprising lymphocytes expressing CD4 and CD25. Therefore, Applicants respectfully submit that the Examiner's rejection of claim 93 (and therefore dependent claims 94 and 95) has been overcome and should be withdrawn.

2. Claim 98

The Examiner has alleged that the specification discloses that cell preparations comprising tolerance inducing cells can comprise about 10-50% of lymphocytes. The Examiner concludes that "[t]he recitation [in the claims] of 'at least 10%' has no upper limit, and has a different scope than the range of 10-50% disclosed by the specification." Office Action at page 4. Applicants respectfully disagree with the Examiner's conclusions. However, solely in order to advance prosecution, and not in acquiescence to the Examiner's rejections, Applicants have amended claim 98 to recite that lymphocytes comprise from about 10% to 50% of the total population of cells in said pharmaceutical composition. Therefore, Applicants respectfully submit that the Examiner's rejection of claim 98 has been rendered moot and should be withdrawn.

3. **Claim 96**

The Examiner has stated that the specification discloses culturing monocytes with 2 to 20 μg/L of M-CSF, but that the instant claims recite that the concentration of M-CSF is 1 to 20 μg/ml. Applicants thank the Examiner for pointing this out, and have amended claim 96 to recite that the M-CSF in the culture medium is 1 to 20 μg/L. Therefore, Applicants respectfully submit that the Examiner's rejection of claim 96 has been rendered moot and should be withdrawn.

B. Rejection Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claim 81 as allegedly being unpatentable under 35 U.S.C. § 112, first paragraph. The Examiner has stated that claim 81 allegedly does not comply with the enablement requirement because the "claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art... to make and/or use the invention." Office Action at page 4. Further, the Examiner alleges that the cell line is required to practice the current invention. It is not. No antibody is required to practice the method of claim 81. The Examiner states that the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines. Applicants respectfully submit that even if the cell line recited in claim 81 was required, the cell line was deposited according to the Budapest Treaty. Applicants have amended the instant specification to include the complete name and address of the depository as well as the date of deposit of the cell line. The recited cell line was deposited on May 13, 2002. Applicants respectfully submit that the Examiner's rejection of claim 81 has been overcome and should be withdrawn.

C. Rejection Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 54, 73-74, 78-81 and 88-99 as allegedly being unpatentable under 35 U.S.C. § 112, first paragraph. The Examiner has stated that claims 54, 73-74, 78-81 and 88-99 allegedly do not comply with the enablement requirement. Applicants respectfully traverse this rejection.

> Applicants thank the Examiner for indicating that the specification is enabling for
>
> a method of treating autoimmune disease comprising administering a CD3+CD14+ cell, wherein the cell is obtained by a process comprising isolating a blood cell population comprising monocytes and lymphocytes, multiplying said cell population with M-CSF, followed by cultivating said cell population with γ-IFN, and a method for treating autoimmune disease comprising administering a cell obtained by a process comprising isolating a blood cell population comprising monocytes and lymphocytes, multiplying said cell population with M-CSF, followed by cultivating said cell population with γ-IFN.

Office Action at page 5.

The Examiner alleges that "the claims encompass treating a wide range of diseases of different etiologies and pathological mechanisms" and that "[i]t is unlikely that a single treatment would be effective for the broad range of diseases encompassed by the instant claims." Office Action at page 6. Applicants respectfully disagree with the Examiner and submit that administration of the presently claimed self-tolerance inducing cells has been demonstrated to be effective in treating diseases associated with disturbed self-tolerance mediated by T cells, such as DSS-induced colitis, in mouse models. *See* Brem-Exner *et al.*, *J Immunol* 180:335-349 (2008), document AG1 in the Information Disclosure Statement submitted herewith. Therefore, Applicants respectfully submit that, contrary to the Examiner's assertions, the claimed invention is effective against the range of diseases. Applicants respectfully submit that the Examiner's rejection of the claims on this basis has been overcome and should be withdrawn.

The Examiner further asserts that the "'prevention' of diseases such as autoimmune disease is highly unpredictable" and concludes that "it would be highly unpredictable as to whether a therapy could be given to a healthy individual in order to prevent any signs or symptoms of disease from ever occurring, as is encompassed by the instant claims." Office Action at page 7. Applicants respectfully disagree with the Examiner and submit that mice treated with a single dose of self-tolerance inducing cells developed colitis at a statistically significant lower rate than untreated animals. *See* Brem-Exner *et al.*, at page 347, column 2. Therefore, as Applicants have demonstrated that treatment with the self-tolerance inducing cells of the present invention results in treatment of DSS-induced colitis in a mouse model, Applicants

respectfully submit that the Examiner's rejection of the claims on this basis has been overcome and should be withdrawn.

In the Office Action at page 7, the Examiner speculates that "it appears likely that the CD3 'expressing' monocytes described by the instant specification are in fact CD3+ monocytes that have acquired CD3/TCR complexes by co-culture with T cells. In fact, the instant specification demonstrates in Example 4 that the expression of CD3 by the monocytic transplantation acceptance inducing cells requires the presence of lymphocytes." The Examiner then concludes that "CD3+CD14+ cells might be generated using other cytokine combinations by co-culture with lymphocytes." Office Action at page 8.

Applicants note that example 4 of the specification as filed discloses cultivation of cell cultures containing only monocytes ("Mo") and containing monocytes and lymphocytes ("Mo+Ly"). Moreover, the specification states that "[d]uring the cultivation, CD14+/CD3+ cells effective as TAIC [transplant acceptance inducing cells] are formed in both cultures." *See* specification as filed at page 44, lines 10-11. However, solely in order to advance prosecution, and not in acquiescence to the Examiner's rejections, Applicants have amended claims 78, 79, 98 and 99 to recite that lymphocytes and granulocytes comprise from about 10% to about 50% of the total population of cells. Applicants respectfully submit that the Examiner's rejection of the claims on this basis has been overcome and should be withdrawn.

The Examiner has alleged that "the generation of monocytes capable of suppressing an immune response is unpredictable and highly dependent on the cell culture conditions employed." Office Action at page 8. The Examiner states that γ-IFN can suppress T cells *in vitro* if it is added simultaneously with M-CSF, but that it does not abrogate the suppressive effect of the monocytic cells if it is added after the M-CSF cultures have already been established. Applicants disagree, but solely to facilitate prosecution, have amended claims 78, 79 and 99 to recite that monocytes are cultivated with γ-IFN after they are cultivated with GM-CSF. Therefore, Applicants respectfully submit that the Examiner's rejection of the claims on this basis has been overcome and should be withdrawn.

In the Office Action at page 8, the Examiner reiterates that "based on the teachings of the specification, obtaining a CD3+CD14+ cell by culturing a pure population of monocytes with M-

CSF and γ-IFN would be extremely unpredictable." As discussed above, Applicants disagree in light of the specification, and have amended claims 78, 79, 98 and 99 to recite that lymphocytes and granulocytes comprise from about 10% to about 50% of the total population of cells. Therefore, Applicants respectfully submit that the Examiner's rejection of the claims on this basis has been overcome and should be withdrawn.

In the Office Action at page 9, the Examiner states that "[t]he specification does not demonstrate that these [CD3+CD14+] cells are responsible for suppressing colitis in vivo, nor does the specification provide evidence that any CD3+CD14+ cell (for example, those derived by transfer of CD3 onto monocytes in a co-culture with T cells in the absence of M-CSF/γ-IFN) are capable of treating autoimmune disease." The Examiner concludes that "the teachings of the specification are not commensurate in scope with the instant claims, which encompass preventing or treating any disease associated with disturbed self-tolerance with any CD14 and CD3 expressing cell, or with a cell made by culturing an isolated monocyte with M-CSF and γ-IFN simultaneously." *Id.* As discussed above, administration of the presently claimed self-tolerance inducing cells has been demonstrated to be effective in treating DSS-induced colitis in mouse models. It is improper to hold Applicants to a higher standard. (*In re Brana*, 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir. 1995) states that "FDA approval... is not a prerequisite for finding a compound useful within the meaning of the patent laws.") Moreover, claims 77, 78 and 99, and their dependents, have been amended to recite that monocytes and lymphocytes are co-cultivated in culture medium containing M-CSF, followed by cultivation in culture medium containing γ-IFN. Therefore, Applicants respectfully submit that the Examiner's rejection of the claims on this basis has been overcome and should be withdrawn.

The Examiner alleges that "the demonstration of a CD3+ monocyte by FACS analysis is not commensurate in scope with the instant claims which encompass any 'CD3 expressing cell.'" Office Action at page 9. The Examiner concludes that "the teachings of the specification are not commensurate in scope with the instant claims, which encompass preventing or treating any disease associated with disturbed self-tolerance with any CD14 and CD3 expressing cell, or with a cell made by culturing an isolated monocyte with M-CSF and γ-IFN simultaneously." *Id.* Applicants respectfully disagree. However, solely in order to advance prosecution, and not in

acquiescence to the Examiner's rejections, Applicants have amended the present claims to recite that lymphocytes and granulocytes comprise from about 10% to 50% of the total population of cells and that said monocytes, lymphocytes and granulocytes are cultured with γ-IFN after they are cultured with M-CSF. Therefore, for at least the reasons stated above, Applicants respectfully submit that the Examiner's rejection of claims 54, 73-74, 78-81 and 88-99 under 35 U.S.C. § 112, first paragraph has been overcome and should be withdrawn.

D. Provisional Rejection on the Ground of Nonstatutory Non-Obviousness Type Double Patenting

The Examiner has provisionally rejected claims 54, 73-74, 78-81 and 88-99 as allegedly being unpatentable over claims 51-52, 74-77 and 84-105 of copending Application No. 10/520,931 ("the '931 application"). The Examiner asserts that "[the method of suppressing transplant rejection reactions comprising administering a cell of monocytic origin that expresses CD3 and CD14 as claimed in the '931 application] would inherently result in the 'prevention' of autoimmune disease, since it is the same as the method of the instant claims." Office Action at page 10. Applicants respectfully disagree. The specification clearly states that "while TAIC [transplant acceptance inducing cells] and STIC [self tolerance inducing cells] are both derived from monocytes by essentially the same process, TAIC are allogeneic to the patient to be treated, while STIC are autologous in this respect." *See* specification as filed at page 11, lines 21-24. However, in order to facilitate prosecution, Applicants are willing to consider submitting a terminal disclaimer in the present case with regard to Application No. 10/520,931 upon an indication of allowable subject matter. As such, Applicants respectfully request that this rejection of claims 54, 73-74, 78-81 and 88-99 be held in abeyance until the Examiner provides an indication of allowable subject matter. Additionally, it is noted that the filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. *See, e.g., Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991) ("filing of a terminal

disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection.").

CONCLUSION

In view of the above, each of the presently pending claims is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue. The Examiner is encouraged to contact the undersigned at (202) 942-6237 should any additional information be necessary for allowance.

Respectfully submitted,

David R. Marsh (Reg. Atty. No. 41,408)
Kristan L. Lansbery (Reg. Atty. No. 53,183)
Julie L. Blum (Reg. Agent No. 61,840)

Date: April 22, 2009

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DSMZ
Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

University of Kiel
Dept. of General & Thoracic Surery
Arnold-Heller-Str. 7
24105 Kiel

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
GM-7	DSM ACC2542

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I. above was accompanied by:

(x) a scientific description
( ) a proposed taxonomic designation

(Mark with a cross where applicable).

III. RECEIPT AND ACCEPTANCE

The International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 2002-05-13 (Date of the original deposit)[1].

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion)

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name:	DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH
Address:	Mascheroder Weg 1b D-38124 Braunschweig

Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):

V. Weiko

Date: 2002-05-22

[1] Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

Form BP/4 (sole page) (DSMZ)

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

DSMZ
Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH

INTERNATIONAL FORM

University of Kiel
Dept. of General & Thoracic Surery
Arnold-Heller-Str. 7
24105 Kiel

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: University of Kiel Dept. of General & Thoracic Surery Address: Arnold-Heller-Str. 7 24105 Kiel	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY DSM ACC2542 Date of the deposit or the transfer[1] 2002-05-13

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 2002-05-13 [2].
On that date, the said microorganism was

(x)[3] viable

( )[3] no longer viable

IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):
Address: Mascheroder Weg 1b D-38124 Braunschweig	V. Weiß Date: 2002-05-22

1 Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
2 In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.
3 Mark with a cross the applicable box.
4 Fill in if the information has been requested and if the results of the test were negative.